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**PATENT** 

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#### **CERTIFICATE OF MAILING**

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Bethany Crandell  Bethany Crandell	Date of Deposit
Applicant: Markou et al.	) ) Art Unit: 1617
Serial No.: 10/527,525	) Examiner: Kendra Carter
I.A. Filing Date: Sep. 10, 2003	) Confirmation No.: 3218
Title: METHODS FOR TREATING DISORDERS ASSOCIATED WITH mGLU RECEPTORS INCLUDING ADDICTION AND DEPRESSION	) Our Ref.: TSRI 897.1 ) ) ) )

# REPLY BRIEF

MAIL STOP: Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

### Dear Sir:

This Reply Brief is submitted in response to the Examiner's Answer, dated July 1, 2010, which was issued in connection with the appeal filed by Appellants on April 7, 2010 in the above-referenced patent application.

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# I. Status of Claims

Claims 1-3, 6-7, 9-10, 14-17, 19, 27-28 and 32 are pending.

Claims 4, 5, 8, 11-13, 18, 20-26, 29-31, and 33 were canceled by Applicants

Claims 10, 14, 15, 17 and 19 are withdrawn from consideration by the Examiner

Claims 1-3, 6, 7, 9, 16, 27, 28 and 32 are rejected.

Claims 1-3, 6, 7, 9, 27, 28 and 32 are on appeal.

# II. Grounds of rejection to be reviewed on appeal

Issue 1. Whether Claims 1-3, 6, 7 and 16 are unpatentable under 35 U.S.C. § 103(a) over Adam et al. (U.S. Patent No. 6,406,094; attached as Ref. 1) in view of Corsi et al. (U.S. Application 2003/0195139; attached as Ref. 2) or Chiamulera et al. (Nat. Neurosci. 4:873-874, 2001; attached as Ref. 3)?

Issue 2. Whether Claims 9, 27, 28 and 32 are unpatentable under 35 U.S.C. § 103(a) over Chiamulera et al. in view of Adam et al.?

### III. Argument

# A. Prior art teaching of treating withdrawal symptoms by mGluR II agonism

In the Examiner's Answer, the Examiner maintains that Adams et al. (U.S. Patent No. 6,406,094) provides a motivation to try group II mGluR <u>antagonists</u> in the treatment of nicotine and opiate addiction. The Examiner takes the position that the skilled artisan would be motivated by the unsubstantiated speculations of Adams et al. while disregarding the clear teaching of using group II mGluR <u>agonists</u> for treating addictive disorders as reported in a number of scientific publications. In support of this view, the Examiner further provided the following comments in the Examiner's Answer.

In regards to the other art showing opposite results, the teaching of Kenny et al. can help to explain the differences. Particularly, Kenny et al. teaches on page 1075, column 1, paragraph 3, that prolonged continuous nicotine exposure increase mGluII receptor function, but decreased exposure to psychostimulants (i.e. opiates) decreased mGlull function. Thus, it is possible that chronic nicotine and psychostimulant (i.e. opiate) administration induce different alterations in glutamatergic transmission. Alternatively, this apparent discrepancy may be explained by the fact that the long-term behavioral effects of drugs of abuse are related to the dosing administration regimen. Further, although Helton et al. teaches that a mGluR II agonist treats nicotine withdrawal symptoms. Helton et al. teaches that Group II mGluR agonist decrease glutamate release (see page 1515, right column, second paragraph, last 6 lines). Helton et al. teaches that the actions of compounds such as LY354740 (the mGluR II agonist) may be altered in the nicotine-dependent animals (see page 1515, right column, last paragraph). Thus, one can not rule out suggested therapeutic teachings of Adams et al. when the effects of chronic nicotine use on mGluR agonist or nicotine modulation of glutamate excitation (i.e. regulation of glutamate release) are not known (as taught by Helton et al., page 1515, right column, first paragraph, last four lines). As the Appellants suggested on page 12 of the Appeal Brief (see paragraph 2), one would understand that inhibition of mGluR2/3 receptors to be the action of an antagonist compound. Thus, a Group II mGluR antagonist would have the same effect as the mGluR agonist because they would both decrease glutamate

**release**. . . . According to the Appellant (see page 12 of the Appeal Brief, second paragraph), Fundytus and Coderre, teach activation of the mGluR receptors could reduce withdrawal symptoms in human patients, which is in contradiction to the teachings of Helton et al. because Helton et al. teach that the agonist decreases glutamate release. [Examiner's Answer, pages 9-10; emphases via bold and italicized fonts added]

The issue in dispute here is whether the prior art would motivate one to use Group II mGluR antagonism for treating addictive disorders. However, Appellants cannot understand how Kenny et al. and Helton et al. as discussed by the Examiner could provide any support to the Examiner's position. First, Kenny et al. is not a prior art reference. Rather, it is a post-priority publication of the present inventors which reported some of the same findings disclosed in the subject patent application. The teaching of Kenny et al. as quoted by the Examiner corresponds to the present inventors' explanation of the apparent difference between the subject disclosure (i.e., treating drug dependence via mGluRII antagonism) and the prior art teaching (i.e., treating withdrawal symptoms via mGluRII agonism). Contrary to what the Examiner apparently implied, Kenny et al. is certainly not prior art that might otherwise motivate a skilled artisan to disregard the prior art teaching of treating drug addictions via mGluRII agonism.

Turning to Helton et al., Appellants do not dispute that Helton et al. teaches that Group II mGluR <u>agonists</u> decrease glutamate release as pointed by the Examiner. However, contrary to the Examiner's assertion (see the bolded sentence in the above-quoted excerpt from the Examiner's Answer), a Group II mGluR <u>antagonist</u> and a GroupII mGluR <u>agonist</u> would NOT have the same effect in decreasing glutamate release. Rather, as Appellants have repeatedly pointed out, antagonism of Group II mGluR receptors (i.e., mGluR2 and mGluR3) would increase glutamate release (while blockade of Group I mGluR receptors such as mGluR5 would decrease glutamate release) (see, e.g., Appeal Brief, page 15, last paragraph). Thus, unlike what the Examiner apparently suggested, the prior art including Helton et al. would not motivate